PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 030833wo/Me/sto	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/03626	International filing date *(day/month/year)* 08.04.2003	Priority date *(day/month/year)* 08.04.2002
International Patent Classification (IPC) or both national classification and IPC C12Q1/68		
Applicant EVOTEC NEUROSCIENCES GMBH et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 9 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.11.2003	27.08.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Hagenmaier, S Telephone No. +49 89 2399-4082

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/03626

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-31 as originally filed

Claims, Numbers

1-21 filed with telefax on 11.08.2004

Drawings, Sheets

1/11-11/11 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority in written form.

   ☒ furnished subsequently to this Authority in computer readable form.

   ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☒ the claims, Nos.: 22

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1,4-7,14,15 (all partially); 2,3,9-13,16-21 (all completely)

   because:

   ☒ the said international application, or the said claims Nos. 15,16,19 (all partially) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☒ the claims, or said claims Nos. 1,4-7,14,15 (all partially); 2,3,11-13,16,19-21 (all completely) are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 9,10,17,18 (all completely)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1,4-7,14,15
	No:	Claims	8
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1,4-8,14,15
Industrial applicability (IA)	Yes:	Claims	1,4-8,14
	No:	Claims	

2. Citations and explanations

see separate sheet

III. Non-establishment of opinion

1. SUBJECT MATTER COVERED BY THE PROVISION OF RULE 67.1 (iv) PCT

Claims 15 and 16 relate to methods which can be understood as to encompass methods for treatment of the human or animal body by surgery or therapy. The subject-matter of claims 15 and 16 is therefore considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be established for these claims in regard to industrial applicability.

Claim 19 (partially) relates to a method which can be understood as to encompass diagnostic methods which are carried out on the human or animal body. The subject-matter of claim 19 is therefore considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT.

2. CLARITY and SUPPORT (ART. 6 PCT)

Claims 1,2,3,6,8,11,14,15,19-21 are not clear: the expression "gene coding for a vault protein, the minor vault protein ADPRTL1," does not clearly limit the scope of the claim to a gene coding for ADPRTL1, it could as well be interpreted as a listing of possibilities. Claims 1,2,3,6,8,11,14,15,19-21 are therefore not clear. However, in view of the description, this expression is interpreted as being limited to a gene coding for the minor vault protein ADPRLT1.

Article 6 PCT requires that the matter for which protection is sought be defined in the claims in a clear and concise manner and that the claims be supported by the description. A claim is considered not to be supported in the sense of Article 6 PCT if the description does not disclose sufficient technical information to allow a person skilled in the art, using his common general knowledge, to carry out the invention within the whole area that is claimed, without undue burden and without using inventive skills. It should be noted that such lack of technical support can also be objected under Art. 5 PCT, the objection being that the disclosure is insufficient to enable the skilled person to carry out the invention over the whole area claimed. The requirements of Articles 5 and 6 PCT are both designed to reflect the principle that the terms of a claim should be commensurate with, or be justified by the disclosure of the invention.

The underlying application describes the identification of the differential expression of

ADPRTL1 in post-mortem brain tissue derived from AD patients compared to non-AD control individuals. An up-regulation of ADPRTL1 gene transcription in the temporal cortex compared to the frontal cortex of Alzheimer patients was detected which was not detectable in non-AD individuals.
The analysis of the differential expression of ADPRTL1 is limited to post-mortem brain tissue collected from AD and non-AD individuals. No experimental data are given demonstrating any differential expression of ADPRTL1 protein.

Claims 1-3,5-7,13,14-16,19-21 relating to *any* neurodegenerative disease are not considered to be supported in the sense of Article 6 PCT: Due to the fact that the molecular mechanisms underlying different neurodegenerative diseases can be of quite different nature, a molecular mechanism only observed in AD cannot credibly be extrapolated to any other neurodegenerative disease. Such teaching would not be accepted by the skilled person as an enabling teaching but just as a mere speculation.

In addition claims 1-7 lack support for the following reasons:
There is no technical teaching disclosed in the description supporting a method according to claim 1 and 4-7 for prognosticating or determining whether a subject is at increased risk of developing Alzheimer's disease, comprising determining a level and/or an activity of a ADPRTL1 gene transcription/ translation product. There is also no technical support in the description for supporting the methods according to claims 2 or 3 and 4-7 for monitoring the progression or of evaluating a treatment for Alzheimer's disease comprising determining a level and/or an activity of a ADPRTL1 gene transcription/ translation product. The description only discloses the differential expression of ADPRTL1 transcripts in post-mortem brain tissue of patients which were already suffering from Alzheimer's disease.

Furthermore, there is no technical teaching in the description nor the drawings which could provide credible support for claims 19-21 and claims 1-7,14-16 insofar as they relate to the determination of the differential expression of ADPRTL1 translation products: Due to the fact that the differential expression of the transcription product of a gene does not necessarily lead to a differential expression of the translation product, the observed differential expression of ADPRTL1 transcription products cannot provide support for the methods claimed insofar as they refer to the detection of the differential expression of ADPRTL1 translation products.

From what is said above, it follows that the subject matter of claim 21, namely the use of an antibody specifically immunoreactive with a translation product of a gene coding

for an ADPRTL1 protein for detecting the pathological state of a cell in a sample from a subject, as well cannot be regarded as being supported as required by Article 6 PCT.

Furthermore, claims 1-7,21 refer to the use of any sample of a subject, yet no technical support can be found in the description for such generalisation: the differential expression of ADPRTL1 mRNA was only demonstrated in specific brain tissue samples, namely in a sample from the frontal cortex and in a sample from the temporal cortex.

Claims 11 and 12 relate to a recombinant non-human animal comprising a non-native ADPRTL1 gene sequence wherein said non-human animal exhibit a predisposition to developing symptoms of neurodegenerative diseases or related disorders. The technical teaching disclosed in the underlying application does however not support such recombinant non-human animal as required by Article 6 PCT. The same reasoning applies for claims 13 and 16 referring to the use of such recombinant animal.

The lack of support for claims 2,3,11-13,16,19-21, and for claims 4-7 insofar as they relate to these claims, is such, that no meaningful opinion can be formed.

An opinion in regard to novelty and inventive step will therefore only be given for those parts of claims 1,4-7 and 14,15 which are considered to be supported by the description, namely methods according to claims 1,4-7 for the diagnosis of AD in post-mortem brain tissue samples comprising determining a differential expression of the ADPRTL1 gene in AD brain tissue compared to non AD tissue wherein an up-regulation of ADPRTL1 mRNA in temporal cortex compared to frontal cortex is indicating AD and an assay according to claims 14 and 15 for screening for a modulator of AD comprising the testing of the level of a transcription product of a gene coding for ADPRTL1.

V. Reasoned statement

1. CITATIONS

Reference is made to the following documents:

D1: KIRCKHOEFER V A ET AL: 'The 193-kD vault protein, VPARP, is a novel poly(ADP-ribose) polymerase' THE JOURNAL OF CELL BIOLOGY, ROCKEFELLER UNIVERSITY PRESS, US, vol. 146, no. 5, 6 September 1999 (1999-09-06), pages 917-928, XP002180527 ISSN: 0021-9525 cited in the application

D2: STILL I H ET AL: 'Identification of a novel gene (ADPRTL1) encoding a potential Poly(ADP-ribosyl)transferase protein.' GENOMICS. UNITED STATES 15 DEC 1999, vol. 62, no. 3, 15 December 1999 (1999-12-15), pages 533-536, XP002233085 ISSN: 0888-7543 cited in the application

D3: WO 99/62547 A (ROME LEONARD H ;UNIV CALIFORNIA (US); KICKHOEFER VALERIE A (US)) 9 December 1999 (1999-12-09) cited in the application

D4: EP-A-1 188 839 (EVOTEC NEUROSCIENCES GMBH) 20 March 2002 (2002-03-20)

2. NOVELTY (Art. 33(2) PCT)

2.2 D1 discloses primers specific for RT-PCR of the p193 mRNA (p. 918, right col., last §; p193 is a synonym of ADPRTL1). D1 as well describes antibodies specific to the p193 protein (p. 919, left col., 4 §).

2.3 D2 discloses hybridizations probes, i.e. IMAGE clone 26760, for the Northern blot analysis of ADPRTL1 (p. 534, left col., second §; Fig. 1).

2.4 D3 discloses antibodies specific to the p193 protein (p. 7, l. 4-8) and the p193 cDNA (Seq. ID 1).

In the light of D1-D3, claim 8 is not novel.

3. Inventive step (Art. 33(3) PCT)

3.1 D4 is considered closest prior art for those parts of claims 1,4-7,14,15 considered to be supported. D4 discloses the use of flotillin mRNA expression as a marker for AD. The flotillin mRNA is differentially expressed in post-mortem brain tissue of AD- patients compared to non-AD individuals wherein the up-regulation of flotillin mRNA in temporal cortex compared to frontal cortex of AD patients is indicating AD. A method for screening for a modulator of AD comprising testing the level of a transcription product of a gene coding for flotillin is disclosed as well.

The difference between the methods disclosed in D4 and the methods claimed in claims 1-7,14,15 is that the ADPRTL1 mRNA expression is used as a marker for AD instead of the flotillin mRNA expression.

Due to the fact that the use of ADPRTL1 mRNA expression as a marker for AD appear not to show any effects going beyond those described in regard to the use of flotillin mRNA expression as a marker for AD, the problem of the underlying application must be seen in the provision of methods as disclosed in D4 using an alternative mRNA which, like flotillin mRNA is differentially expressed in specific post-mortem brain tissue samples, i.e. in the temporal cortex compared to frontal cortex of AD patients compared to non-AD individuals for use as a marker for AD.

The solution is the use of the ADPRTL1 mRNA expression as a marker.

A person skilled in the art trying to solve the problem posed would try to identify further mRNAs being differentially expressed in specific post-mortem brain tissue samples, i.e. in the temporal cortex compared to the frontal cortex of AD-patients compared to non-AD individuals, for use as an alternative marker for AD. Due to the fact that a person skilled in the art is aware that differences in the mRNA expression observed in different tissues under different physiological conditions encompass many different mRNAs and due to the fact that the identification of mRNAs differentially expressed in the temporal cortex compared to frontal cortex in AD and non-AD individuals is already described in D4, a person skilled in the art would have tried with a reasonable expectation of success to identify further such differentially expressed mRNAs without using inventive skills in order to solve the problem posed. The identification/provision of differentially expressed ADPRTL1 mRNA and the use of the ADPRTL1 mRNA expression as a marker for AD is therefore considered not to involve an inventive step because the identification of

ADPRTL1 mRNA being differentially expressed is just an arbitrary choice of several mRNAs the person skilled in the art would have expected to identify as being differentially expressed in the same way as flotillin mRNA.

Therefore, insofar as having been examined, the subject matter of claims 1, 4-7,14,15 is not considered to involve an inventive step.

10/510506
DT05 Rec'd PCT/PTO 07 OCT 2004

AMENDED CLAIMS

1. A method of diagnosing or prognosticating a neurodegenerative disease in a subject, or determining whether a subject is at increased risk of developing said disease, comprising:
determining a level and/or an activity of
(i) a transcription product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or
(ii) a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or
(iii) a fragment, or derivative, or variant of said transcription or translation product
in a sample obtained from said subject and comparing said level and/or said activity to a reference value representing a known disease or health status, thereby diagnosing or prognosticating said neurodegenerative disease in said subject, or determining whether said subject is at increased risk of developing said neurodegenerative disease.

2. A method of monitoring the progression of a neurodegenerative disease in a subject, comprising:
determining a level and/or an activity of
(i) a transcription product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or
(ii) a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or
(iii) a fragment, or derivative, or variant of said transcription or translation product
in a sample obtained from said subject and comparing said level and/or said activity to a reference value representing a known disease or

health status, thereby monitoring the progression of said neurodegenerative disease in said subject.

3. A method of evaluating a treatment for a neurodegenerative disease, comprising:
determining a level and/or an activity of
(i) a transcription product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or
(ii) a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or
(iii) a fragment, or derivative, or variant of said transcription or translation product,
in a sample obtained from a subject being treated for said disease and comparing said level and/or said activity to a reference value representing a known disease or health status, thereby evaluating said treatment for said neurodegenerative disease.

4. The method according to any of claims 1 to 3 wherein said neurodegenerative disease is Alzheimer's disease.

5. The method according to any of claims 1 to 4 wherein said sample comprises a cell, or a tissue, or a body fluid, in particular cerebrospinal fluid or blood.

6. The method according to any of claims 1 to 5 wherein said reference value is that of a level and/or an activity of
(i) a transcription product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or
(ii) a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or
(iii) a fragment, or derivative, or variant of said transcription or translation product,

in a sample obtained from a subject not suffering from said neurodegenerative disease.

7. The method according to any of claims 1 to 6 wherein an alteration in the level and/or activity of a transcription product of the gene coding for the minor vault protein ADPRTL1 and/or a translation product of a gene coding for the minor vault protein ADPRTL1, and/or a fragment, or derivative, or variant thereof, in a sample cell, or tissue, or body fluid, in particular cerebrospinal fluid, obtained from said subject relative to a reference value representing a known health status indicates a diagnosis, or prognosis, or increased risk of Alzheimer's disease in said subject.

8. A kit for diagnosing or prognosticating a neurodegenerative disease, in particular Alzheimer's disease, in a subject, or determining the propensity or predisposition of a subject to develop such a disease by:
(i) detecting in a sample obtained from said subject a level, or an activity, or both said level and said activity of a transcription product and/or of a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1, compared to a reference value representing a known health status; and said kit comprising:
a) at least one reagent which is selected from the group consisting of (i) reagents that selectively detect a transcription product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and (ii) reagents that selectively detect a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1.

9. A method of treating or preventing a neurodegenerative disease, in particular AD, in a subject comprising administering to said subject in a therapeutically or prophylactically effective amount an agent or agents which directly or indirectly affect an activity and/or a level of

(i) a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(ii) a transcription product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(iii) a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(iv) a fragment, or derivative, or variant of (i) to (iii).

10. A modulator of an activity and/or of a level of at least one substance which is selected from the group consisting of

(i) a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(ii) a transcription product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(iii) a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(iv) a fragment, or derivative, or variant of (i) to (iii).

11. A recombinant, non-human animal comprising a non-native gene sequence coding for a vault protein, the minor vault protein ADPRTL1, or a fragment, or a derivative, or a variant thereof, said animal being obtainable by:

(i) providing a gene targeting construct comprising said gene sequence and a selectable marker sequence, and

(ii) introducing said targeting construct into a stem cell of a non-human animal, and

(iii) introducing said non-human animal stem cell into a non-human embryo, and

(iv) transplanting said embryo into a pseudopregnant non-human animal, and

(v) allowing said embryo to develop to term, and

(vi) identifying a genetically altered non-human animal whose genome comprises a modification of said gene sequence in both alleles, and

(vii) breeding the genetically altered non-human animal of step (vi) to obtain a genetically altered non-human animal whose genome comprises a modification of said endogenous gene, wherein said disruption results in said non-human animal exhibiting a predisposition to developing symptoms of a neurodegenerative disease or related diseases or disorders.

12. The animal according to claim 11 wherein said minor vault protein ADPRTL1 is the minor vault protein of SEQ ID NO. 2.

13. Use of the recombinant, non-human animal according to claim 11 or 12 for screening, testing, and validating compounds, agents, and modulators in the development of diagnostics and therapeutics to treat neurodegenerative diseases, in particular Alzheimer's disease.

14. An assay for screening for a modulator of neurodegenerative diseases, in particular Alzheimer's disease, or related diseases or disorders of one or more substances selected from the group consisting of

(i) a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(ii) a transcription product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(iii) a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(iv) a fragment, or derivative, or variant of (i) to (iii), said method comprising:

(a) contacting a cell with a test compound;

(b) measuring the activity and/or level of one or more substances recited in (i) to (iv);

(c) measuring the activity and/or level of one or more substances recited in (i) to (iv) in a control cell not contacted with said test compound; and

(d) comparing the levels and/or activities of the substance in the cells of step (b) and (c), wherein an alteration in the activity and/or level of substances in the contacted cells indicates that the test compound is a modulator of said diseases or disorders.

15. A method of screening for a modulator of neurodegenerative diseases, in particular Alzheimer's disease, or related diseases or disorders of one or more substances selected from the group consisting of

(i) a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(ii) a transcription product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(iii) a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(v) a fragment, or derivative, or variant of (i) to (iii), said method comprising:

(a) administering a test compound to a test animal which is predisposed to developing or has already developed symptoms of a neurodegenerative disease or related diseases or disorders in respect of the substances recited in (i) to (iv);

(b) measuring the activity and/or level of one or more substances recited in (i) to (iv);

(c) measuring the activity and/or level of one or more substances recited in (i) or (iv) in a matched control animal

which is predisposed to developing or has already developed symptoms of a neurodegenerative disease or related diseases or disorders in respect to the substances recited in (i) to (iv) and to which animal no such test compound has been administered;

(d) comparing the activity and/or level of the substance in the animals of step (b) and (c), wherein an alteration in the activity and/or level of substances in the test animal indicates that the test compound is a modulator of said diseases or disorders.

16. The method according to claim 15 wherein said test animal and/or said control animal is a recombinant animal which expresses a vault protein, the minor vault protein ADPRTL1 or a fragment, or a derivative, or a variant thereof, under the control of a transcriptional control element which is not the native vault protein gene transcriptional control element.

17. An assay for testing a compound, preferably for screening a plurality of compounds for inhibition of binding between a ligand and a vault protein, the minor vault protein ADPRTL1 or a fragment, or derivative, or a variant thereof, said assay comprising the steps of:

(i) adding a liquid suspension of said vault protein, or a fragment, or a derivative, or a variant thereof, to a plurality of containers;

(ii) adding a compound, preferably a plurality of compounds, to be screened for said inhibition of binding to said plurality of containers;

(iii) adding a detectable ligand, in particular a fluorescently detectable ligand, to said containers;

(iv) incubating the liquid suspension of said vault protein, or said fragment, or derivative, or variant thereof, and said compound, preferably said plurality of compounds, and said ligand;

(v) measuring amounts of detectable ligand or fluorescence associated with said vault protein, or with said fragment, or derivative, or variant thereof; and

(vi) determining the degree of inhibition by one or more of said compounds of binding of said ligand to said vault protein, or said fragment, or derivative, or variant thereof.

18. An assay for testing a compound, preferably for screening a plurality of compounds to determine the degree of binding of said compounds to a vault protein, the minor vault protein ADPRTL1, or to a fragment, or derivative, or variant thereof, said assay comprising the steps of:

(i) adding a liquid suspension of said vault protein, or a fragment, or derivative, or variant thereof, to a plurality of containers;

(ii) adding a detectable compound, preferably a plurality of detectable compounds, in particular fluorescently detectable compounds, to be screened for said binding to said plurality of containers;

(iii) incubating the liquid suspension of said vault protein, or said fragment, or derivative, or variant thereof, and said compound, preferably said plurality of compounds;

(iv) measuring amounts of detectable compound or fluorescence associated with said vault protein, or with said fragment, or derivative, or variant thereof; and

(v) determining the degree of binding by one or more of said compounds to said vault protein, or said fragment, or derivative, or variant thereof.

19. Use of a protein molecule, said protein molecule being a translation product of the gene coding for a vault protein, the minor vault protein ADPRTL1, SEQ ID NO. 2, or a fragment, or derivative, or variant thereof, as a diagnostic target for detecting a neurodegenerative disease, preferably Alzheimer's disease.

20. Use of a protein molecule, said protein molecule being a translation product of the gene coding for a vault protein, the minor vault protein ADPRTL1, SEQ ID NO. 2, or a fragment, or derivative, or variant thereof, as a screening target for reagents or compounds preventing, or treating, or ameliorating a neurodegenerative disease, preferably Alzheimer's disease.

21. Use of an antibody specifically immunoreactive with an immunogen, wherein said immunogen is a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1, SEQ ID NO. 2, or a fragment, or derivative, or variant thereof, for detecting the pathological state of a cell in a sample obtained from a subject, comprising immunocytochemical staining of said cell with said antibody, wherein an altered degree of staining, or an altered staining pattern in said cell compared to a cell representing a known health status indicates a pathological state of said cell, and wherein said pathological state relates to a neurodegenerative disease, in particular Alzheimer's disease.